

Omalizumab improves asthma-related quality of life in patients with severe allergic asthma

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Background: We have previously shown that omalizumab, a recombinant humanized monoclonal anti-IgE antibody, reduces asthma exacerbations and decreases inhaled corticosteroid (ICS) requirement in patients with severe allergic asthma who were symptomatic despite moderate-to-high doses of ICSs.

Objective: The aim of the present study was to assess the effects of omalizumab on asthma-related quality of life (QOL).

Methods: These analyses were part of a multicenter, 52-week, randomized, double-blind, placebo-controlled study assessing the efficacy, safety, and tolerability of subcutaneous omalizumab (≥ 0.016 mg/kg of IgE [in international unit per milliliter] per 4 weeks) in 525 adults with severe allergic asthma. A 16-week steroid-stable phase was followed by a 12-week steroid-reduction phase and a 24-week double-blind extension phase. The effect of treatment on asthma-related QOL was evaluated by using the Asthma Quality of Life Questionnaire (AQLQ) administered at baseline and at weeks 16, 28, and 52.

Results: The 2 treatment groups were comparable in terms of baseline AQLQ scores. At weeks 16, 28, and 52, omalizumab-treated patients demonstrated statistically significant improvements across all AQLQ domains, as well as in overall score. Moreover, a greater proportion of patients receiving omalizumab achieved a clinically meaningful improvement in asthma-related QOL during each phase of the study. Greater than 50% of both patients and investigators rated treatment similarly with omalizumab as excellent or good compared with less than 40% of placebo recipients.

Conclusion: In patients requiring moderate-to-high doses of ICSs for severe allergic asthma, the measurably improved disease control afforded by add-on omalizumab therapy is paralleled by clinically meaningful improvements in asthma-related QOL. (*J Allergy Clin Immunol* 2003;111:278-84.)

Key words: Asthma, anti-IgE, omalizumab, quality of life

Asthma has a profound influence on daily quality of life (QOL), not only in terms of symptoms and the risk of serious exacerbations but also in limitation of activities, sleep impairment, and emotional functioning.¹ The extent of such impairment, however, cannot be captured accurately by conventional clinical indices. As such, clinicians and researchers have begun to take a more comprehensive view of the effects of asthma and its treatment on QOL, as seen by the increasing use of QOL instruments in asthma clinical trials.¹

Allergic factors are causal in greater than 90% of patients with asthma.² Pivotal to the underlying pathophysiology is allergen binding to IgE on the surface of effector cells, which causes the release of proinflammatory mediators.³⁻⁷ Targeting of IgE therefore represents a novel approach to the development of new therapeutic agents for the treatment of allergic asthma. Additionally, prevention of the allergic cascade might bring about clinical benefits in other IgE-mediated allergic (atopic) diseases that often coexist in patients with allergic asthma.⁸

Omalizumab (Xolair), a recombinant humanized monoclonal anti-IgE antibody,⁹ is the first anti-IgE agent to undergo clinical evaluation in the treatment of atopic diseases.¹⁰ This agent complexes with unbound free IgE, which prevents its binding to high- and low-affinity receptors on effector cells and thereby attenuates the allergic cascade.¹¹⁻¹³ Indeed, the marked reduction in serum free IgE after administration of omalizumab to patients with allergic asthma¹⁴ is associated with diminution of both the early and late asthmatic responses to inhaled allergen.¹⁵

It has been reported recently that subcutaneous omalizumab improved asthma control and permitted a significant reduction in the use of inhaled corticosteroids (ICSs) in a large placebo-controlled trial in patients with severe allergic asthma who were symptomatic despite moderate-to-high doses of ICSs.¹⁶ Here we report the findings of the effect of omalizumab on asthma-related QOL, which was evaluated in parallel with clinical indices in the same trial.

METHODS

Study design and patients

These analyses were conducted as part of a multicenter, 28-week, randomized, double-blind, placebo-controlled core study with an additional 24-week double-blind extension phase to assess

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TABLE I. Demographics and baseline clinical characteristics (all randomized patients)

	Omalizumab (n = 268)	Placebo (n = 257)
Sex, n (%)		
Male	104 (38.8)	111 (43.2)
Female	164 (61.2)	146 (56.8)
Mean age, y (range)	39.3 (12-73)	39.0 (12-74)
Mean duration of asthma, y (range)	20.6 (1-61)	22.7 (2-60)
Mean BDP dose, $\mu\text{g}/\text{d}$ (range)	569.5 (420-1008)	567.8 (336-840)
Mean serum total IgE level, IU/mL (range)	172.5 (20-860)	186.3 (21-702)
Mean FEV ₁ , % predicted (range)	68.2 (30-112)	67.7 (32-111)
Severe persistent asthma,* n (%)	266 (99.3)	256 (99.6)
Mean AQLQ domain scores		
Activities	4.2	4.3
Emotions	4.0	4.1
Symptoms	4.0	4.1
Environmental exposure	4.0	4.0
Overall score	4.0	4.2

*Asthma severity is based on National Heart, Lung, and Blood Institute guidelines.¹⁹

Abbreviations used

AQLQ: Asthma Quality of Life Questionnaire
BDP: Beclomethasone dipropionate
ICS: Inhaled corticosteroid
QOL: Quality of life

the efficacy, safety, and tolerability of subcutaneous omalizumab in adolescents and adults with severe allergic asthma. The protocol and main clinical-tolerability findings for the core study are reported in full elsewhere.¹⁶ Briefly, patients aged 12 to 75 years who were symptomatic despite moderate-to-high doses of ICSs were enrolled in the study. Eligible patients had asthma for at least 1 year, with serum total IgE levels of 30 to 700 IU/mL and a positive skin prick test response to at least one common allergen (house dust mite, dog, or cat).

After a screening visit, patients commenced a run-in period of 4 to 6 weeks during which all were switched to inhaled beclomethasone dipropionate (BDP), and the dose was adjusted to maintain the previous level of asthma control. The patients were monitored to ensure both the presence of asthma symptoms at levels acceptable to the patients and investigators and patient safety. Patients were maintained on this dose for the final 4 weeks of the run-in period (baseline), on completion of which they were randomized to subcutaneous treatment with either placebo or omalizumab every 2 or 4 weeks (≥ 0.016 mg/kg IgE [in international units per milliliter] per 4 weeks) for 28 weeks. The optimized dose of BDP was maintained for the first 16 weeks of the study (steroid-stable phase). During the following 12 weeks (steroid-reduction phase), the BDP dose was reduced by 25% every 2 weeks over the first 8 weeks until the lowest dose required for asthma control was achieved. Patients were subsequently maintained on the lowest effective dose of BDP for the remaining 4 weeks. The use of rescue inhaled albuterol was permitted throughout the core study; no other asthma medication was allowed.

The 28-week core study was followed by a 24-week double-blind extension phase during which patients continued to receive randomized treatment and the lowest effective dose of BDP (which could be adjusted if required). During this extension phase, investigators were allowed, when judged necessary, to prescribe additional asthma medication, to switch patients to other asthma medications, or both.

QOL assessment

Asthma-related QOL was evaluated at baseline and at the end of the steroid-stable, steroid-reduction, and extension phases (weeks 16,

28, and 52, respectively) by using the 32-item Juniper Asthma Quality of Life Questionnaire (AQLQ).¹⁷ Each question was answered by the patient on a 7-point scale, with a score of 1 representing the greatest impairment and a score of 7 representing no impairment during the past 2 weeks (lower AQLQ scores therefore reflect increased impairment). Items were equally weighted and reported as the mean score for each domain (activity limitations, emotions, symptoms, and exposure to environmental stimuli) along with an overall score.

Treatment effectiveness

On completion of the steroid-reduction phase (week 28), patient and investigator global evaluations of treatment effectiveness were determined as excellent (complete control of asthma), good (marked improvement), moderate (discernible but limited improvement), poor (no appreciable change), or worse.

Statistical analysis

Differences between treatment groups were evaluated by using an analysis of covariance model. The primary analysis was change from baseline for each domain score at the end of the steroid-stable, steroid-reduction, and extension phases. Differences were considered statistically significant at the .05 level (2-sided). For patients who dropped out before the end of the study, scores of the last completed questionnaire were used (last observation carried forward). Further analyses were completed to determine the percentage of patients in each treatment group achieving a clinically meaningful improvement in asthma-related QOL, defined as a change from baseline in domain or overall score of 0.5 points or greater.¹⁸ The percentage of patients who achieved an increase in score of 1.5 points or greater relative to baseline, representing a large improvement in asthma-related QOL,¹⁸ was also determined. The between-group analyses of patient and investigator global evaluations of treatment effectiveness were performed by using the generalized Cochran-Mantel-Haenszel (van Elteren) test stratified by treatment schedule.

RESULTS

A total of 525 patients were randomized to study medication in the 28-week core study (omalizumab, n = 268; placebo, n = 257). Nineteen (7.1%) patients receiving omalizumab and 34 (13.2%) placebo recipients withdrew prematurely. Unsatisfactory therapeutic effect (1 vs 14), withdrawal of consent (7 vs 11), administrative problems (4 vs 2), and loss to follow-up (4 vs 4) were the most

Asthma, rhinitis,
other respiratory
diseases

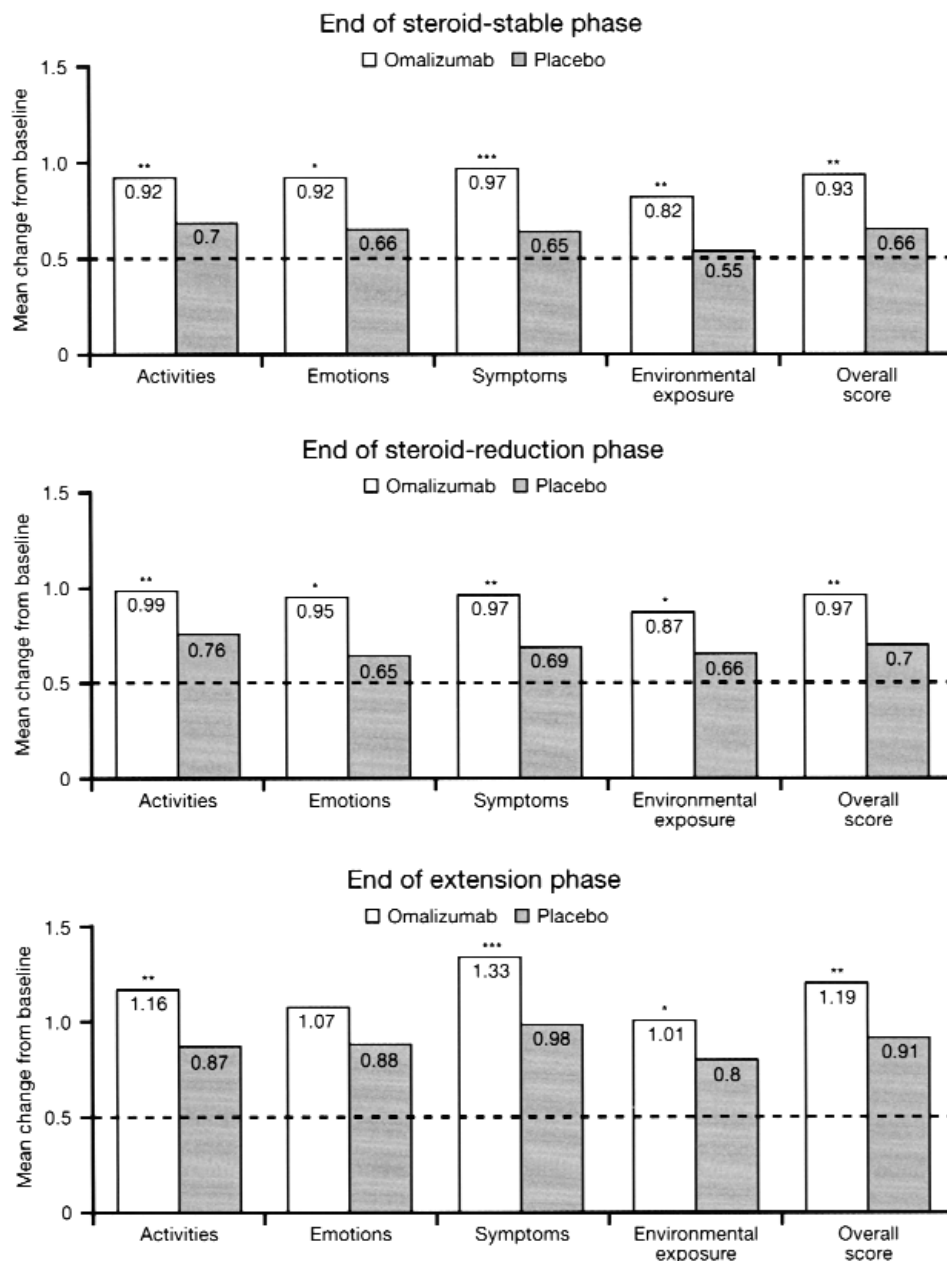


FIG 1. Least-square mean change from baseline in asthma-related QOL scores, as determined by using the Juniper AQLQ,¹⁷ during treatment with omalizumab or placebo in patients with severe allergic asthma. An increase in score of 0.5 points or greater from baseline indicates a clinically significant improvement.¹⁸ * $P < .05$, ** $P < .01$, and *** $P < .001$ versus placebo.

common reasons for early termination in the omalizumab and placebo groups, respectively.

Some 460 patients (omalizumab, $n = 245$; placebo, $n = 215$) continued into the 24-week double-blind extension, of which 20 (4.3%) withdrew prematurely (omalizumab, $n = 12$; placebo, $n = 8$). Administrative problems (omalizumab, $n = 8$; placebo, $n = 1$) and withdrawal of consent (omalizumab, $n = 1$; placebo, $n = 5$) were the most frequent causes of premature study withdrawal during the extension phase.

Overall, the 2 treatment groups were well matched in terms of demographics and clinical characteristics at baseline, including mean AQLQ scores (Table I).¹⁹

Effect of omalizumab on asthma-related QOL

There was significant improvement in AQLQ scores of the omalizumab therapy group in all 4 domains, as well as improvement in overall score during the steroid-stable, steroid-reduction, and extension phases when compared with scores in the placebo group (Fig 1). The improve-

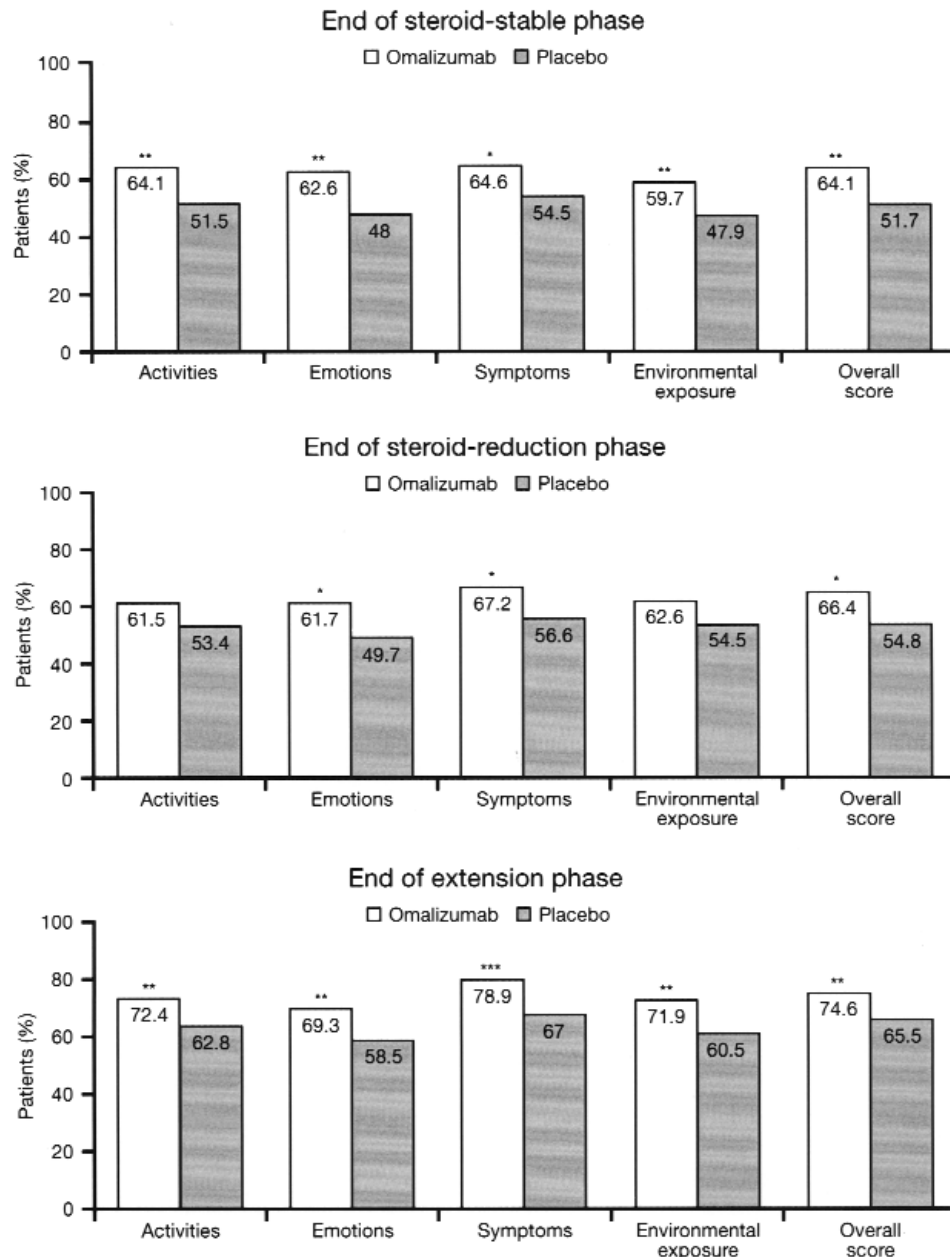


FIG 2. Proportion of patients achieving a clinically meaningful improvement in asthma-related QOL (defined as an increase in score of ≥ 0.5 points from baseline¹⁸) on completion of each phase of the study. * $P < .05$, ** $P < .01$, and *** $P < .001$ versus placebo.

ment in AQLQ scores paralleled the improved asthma control conferred by omalizumab therapy in this study.¹⁶ Moreover, a greater proportion of patients receiving omalizumab achieved a clinically meaningful improvement (≥ 0.5 points from baseline) in asthma-related QOL during each phase of the study (Fig 2). In terms of a large improvement in AQLQ scores (≥ 1.5 points from baseline), the proportion of patients achieving this level of improvement while receiving omalizumab was also higher than that observed for placebo across all 4 AQLQ domains and in terms of overall score (Fig 3).

Treatment effectiveness

The improvement in asthma-related QOL during omalizumab therapy was consistent with patient and investigator opinions of treatment effectiveness at the end of the core study, which showed significant superiority for omalizumab relative to placebo. Greater than 50% of patients and investigators considered treatment with omalizumab to be excellent or good compared with less than 40% receiving placebo (Fig 4). Treatment was rated as poor or worse twice as often in the placebo group as in the active group.

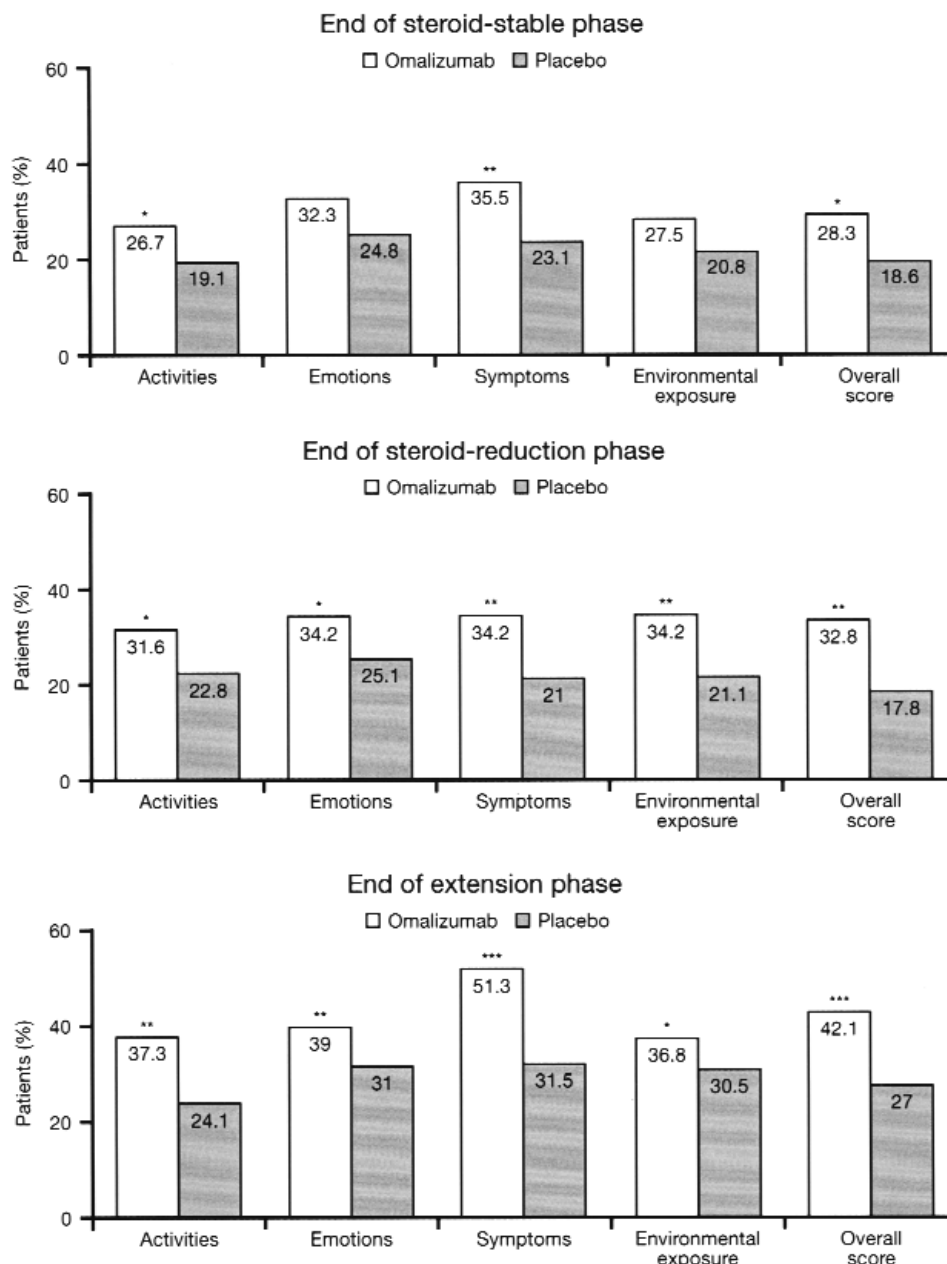


FIG 3. Proportion of patients achieving a large improvement in QOL scores (defined as an increase in score of ≥ 1.5 points from baseline¹⁸) during treatment with omalizumab or placebo in patients with severe allergic asthma. * $P < .05$, ** $P < .01$, and *** $P < .001$ versus placebo.

DISCUSSION

Asthma is a chronic disease that can result in significant impairment of physical and psychosocial well-being in affected individuals. A thorough QOL assessment, in parallel with routine clinical evaluations, should therefore form an important aspect of determining the treatment response in asthma clinical trials. In the present trial data from a validated asthma-specific QOL instrument demonstrated clearly a significant improvement over the 1-year course of the study for patients receiving

anti-IgE therapy with omalizumab. Furthermore, this improvement was significantly greater across each AQLQ domain (activities, emotions, symptoms, and environmental exposure), as well as for overall score compared with placebo.

Previous analyses of the AQLQ have determined that a 0.5-point improvement or greater in domain-overall score is clinically meaningful from the patient's perspective.¹⁸ During each phase of the present study, it is evident that, compared with placebo, a significantly greater percentage of patients receiving omalizumab achieved

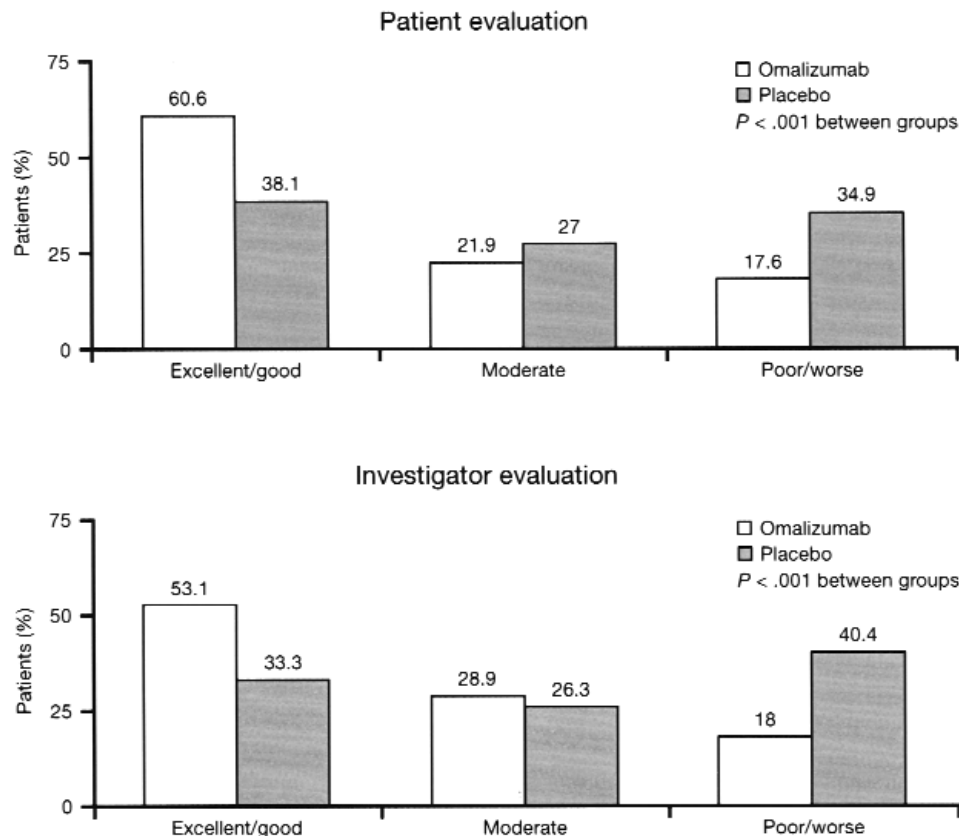


FIG 4. Patient and investigator global evaluations of treatment effectiveness after 28 weeks' treatment with omalizumab or placebo in patients with severe allergic asthma.

clinically meaningful improvement in asthma-related QOL. It is noteworthy that the clinically relevant improvement in asthma-related QOL with omalizumab was achieved alongside a significant reduction in reliance on ICS therapy (median BDP dose reduction of 75% vs 50% for patients receiving placebo, $P < .001$),¹⁶ with significantly fewer mean number of asthma exacerbations per patient during the steroid-stable (0.28 vs 0.54, $P = .006$), steroid-reduction (0.39 vs 0.66, $P = .003$), and extension (0.60 vs 0.83, $P = .023$) phases.^{16,20} Such findings, which are consistent with omalizumab targeting a cause of the underlying allergic disease, were accompanied by improvements in both daytime and nocturnal asthma symptoms and pulmonary function, along with a reduction in use of rescue bronchodilators.¹⁶ Taken together, these findings indicate that the enhanced asthma control afforded by omalizumab therapy leads to a clinically significant parallel improvement in asthma-related QOL.

As observed for the clinical assessment of treatment efficacy,¹⁶ some patients receiving placebo achieved considerable improvements in asthma-related QOL. This high placebo response might be explained by improved compliance with BDP treatment (eg, because of repeated encouragement to adhere to therapeutic regimens and close monitoring by the clinical research team) and

therefore reflects the very best level of outcome that current treatment could possibly achieve. It is notable that add-on therapy with omalizumab still permitted a significant improvement in both disease control and asthma-related QOL against this background. Such findings indicate a potential place for add-on omalizumab therapy in those patients whose symptoms are poorly controlled despite optimal therapy and good compliance.

Both adolescent (aged ≥ 12 years) and adult patients with severe allergic asthma were enrolled in the present study, which gave rise to a methodologic issue because both adult¹⁷ and pediatric²¹ versions of the AQLQ are available. However, to avoid logistics problems, the adult version of the AQLQ was used exclusively in the present trial. Subsequent validation analysis showed that the exclusion of the 41 enrolled patients aged 12 to 17 years, who were evenly distributed between the 2 groups, had no effect on the overall results of the present study. Although the number of enrolled adolescent patients was small, such findings suggest that the use of the adult version of the AQLQ among adolescents was acceptable and did not bias the overall study findings.

With any injection-based therapy, it is important to consider the potential effect of factors, such as injection frequency and risk of local reactions, especially pain, on QOL. In the present study, however, the fact that oma-

lizumab therapy was highly rated by patients would seem to suggest that any negative effect of regular subcutaneous injections is markedly offset by the clinical, and in turn QOL, benefit that patients experience.

In conclusion, the results of the present study show that add-on therapy with omalizumab leads to a clinically meaningful improvement in all aspects of asthma-related QOL for patients requiring moderate-to-high doses of ICSs for severe allergic asthma. These improvements paralleled our previously reported findings of improved disease control and significant reduction in ICS use during omalizumab therapy.¹⁶ Such findings indicate that omalizumab represents a promising new agent for the treatment of allergic asthma and might be particularly useful in those patients with persistent and severe impairment in asthma-related QOL receiving conventional ICS treatment.

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APPENDIX

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